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Nifedipine inhibits superoxide production induced by pulsatile stretch in human aortic endothelial cells

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Abstract: Dihydropyridine calcium channel blocker nifedipine restores nitric oxide-mediated vasodilation in human hypertension. The mechanisms involved have not been fully characterized but may relate to endothelial protection. Mechanical forces such as pulsatile stretch are involved in superoxide anion production. To clarify the effect of nifedipine on the balance between nitric oxide and superoxide anion, human cultured aortic endothelial cells were exposed to pulsatile stretch in the presence and in the absence of this compound. Rhythmic stretching was given for 1 hour by a computerized Flexercell strain unit (10% average elongation, 50 cycles per minute). Superoxide anion production was measured as the superoxide dismutase-inhibitable reduction of cytochrome c. Stretch-induced production of superoxide anion was inhibited in a concentration-dependent manner by nifedipine [6.2 ± 0.9 vs $2.1 \pm 0.6^*$ and $4.8 \pm 0.4^*$, $2.4 \pm 0.5^*$ nmol/60 min/105 cells for stretch vs control and stretch plus nifedipine (10^{-7} and 10^{-6} M), respectively; $n=6$; $*P<0.05$ vs stretch]. This antioxidant activity of nifedipine may exert vascular protective effects in human endothelial cells. Thus, nifedipine may affect mechanical forces which, as determinants of the balance between nitric oxide and superoxide anion, are likely to play a key role in the pathophysiology of hypertensive vascular disease

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REGIONAL INACTIVATION AND SEQUESTRATION OF NITRIC OXIDE (NO) AS NITROTYROSINE IN AORTIC COARCTATION-INDUCED HYPERTENSION (HTN)

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Abdominal aortic coarctation above renal arteries leads to severe HTN above the stenotic site. We have recently shown marked up-regulations of endothelial NO synthase (eNOS) in heart and thoracic aorta, of neuronal (n)NOS in the brain and of eNOS, nNOS and constitutively expressed inducible NOS (iNOS) in the kidneys of rats with severe aortic coarctation above renal arteries. We hypothesize that presence of severe HTN in the face of marked up-regulation of NO system may be due to enhanced NO inactivation by reactive oxygen species (ROS) leading to depressed bioavailability of NO. To test this hypothesis, we determined tissue nitrotyrosine (which is the footprint of NO interaction with ROS) in sham-operated control and aortic banded (above renal arteries) rats four weeks postoperatively. The nitrotyrosine was measured by Western blot analysis using polyclonal antibody. As expected the banded group showed a marked rise in arterial blood pressure measured directly through a carotid canula (203 ± 9 vs 131 ± 2 mmHg, $p < 0.01$). Compared with the sham-operated controls, the banded animals exhibited significant increases in nitrotyrosine abundance in the heart ($279 \pm 47\%$, $p < 0.01$), brain ($164 \pm 12\%$, $p < 0.01$) and the aorta segment above the stricture ($197 \pm 12\%$, $p < 0.01$). In contrast, nitrotyrosine abundance showed only a slight increase in the kidney ($113 \pm 3\%$, $p < 0.05$) and no change in abdominal aorta segment below the stricture ($92 \pm 3\%$, $p > 0.05$) wherein blood pressure was reduced.

In conclusion coarctation-induced hypertension is associated with increased nitrotyrosine abundance in all tissues exposed to high arterial pressure, denoting enhanced inactivation and sequestration of NO in these sites. This can account for development of severe regional HTN despite compensatory up-regulation of NO system as previously shown by us in this model. The absence of nitrotyrosine accumulation in the aorta segment below the stricture wherein blood pressure is reduced, points to the role of baromechanical factors in this process since circulating humoral factors were necessarily similar in both segments.

Key Words: Hypertension; aortic banding; coarctation; nitrotyrosine; reactive oxygen species

DNP-AN ENDOTHELIAL CELL DERIVED MEMBER OF THE NATRIURETIC PEPTIDE FAMILY

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DNP is a potent 38 amino acid peptide isolated from the *Dendroaspis angusticeps* which shares structural similarity with ANP, BNP and CNP as it possesses a 17 amino acid ring structure. Recently, we have reported DNP-like immunoreactivity in human plasma with elevation in congestive heart failure achieving concentrations similar to CNP, an endothelial cell-derived peptide. The goal of the current

study was to determine the presence and secretion of DNP in cultured human aortic endothelial cells and its ability to activate cGMP compared to other known natriuretic peptides (NPs). The rationale for these studies was based upon preliminary studies which have detected DNP-like immunoreactivity associated with isolated blood vessels. Immunohistochemistry utilizing a specific DNP antibody revealed markedly positive endothelial cell granular staining which was localized to the perinuclear position. Staining for non-immune control was negative. Utilizing a specific radioimmunoassay for DNP, we found that DNP was present at a concentration of 82.2 ± 1.2 pg/ml. To determine the biological actions of DNP upon endothelial cell cGMP generation, we stimulated ECs with DNP at 1nM, 10 nM, 100 nM, and 1μM for 60 minutes and compared its action to other NPs. All NPs increased cellular cGMP generation with DNP being the most potent stimulator ($p < 0.05$). The potency of the NPs to stimulate EC cGMP production was $\text{DNP} > \text{ANP} > \text{BNP} > \text{CNP}$. The current studies report for the first time presence and secretion of DNP in human endothelial cells together with documented potent cGMP generating actions. We conclude that DNP may be an additional potent cGMP generating CV peptide of endothelial origin.

Key Words: Natriuretic peptide; DNP; HAEC

NIFEDIPINE INHIBITS SUPEROXIDE PRODUCTION INDUCED BY PULSATILE STRETCH IN HUMAN AORTIC ENDOTHELIAL CELLS

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Dihydropyridine calcium channel blocker nifedipine restores nitric oxide-mediated vasodilation in human hypertension. The mechanisms involved have not been fully characterized but may relate to endothelial protection. Mechanical forces such as pulsatile stretch are involved in superoxide anion production. To clarify the effect of nifedipine on the balance between nitric oxide and superoxide anion, human cultured aortic endothelial cells were exposed to pulsatile stretch in the presence and in the absence of this compound. Rhythmic stretching was given for 1 hour by a computerized Flexercell strain unit (10% average elongation, 50 cycles per minute). Superoxide anion production was measured as the superoxide dismutase-inhibitable reduction of cytochrome c. Stretch-induced production of superoxide anion was inhibited in a concentration-dependent manner by nifedipine [6.2 ± 0.9 vs $2.1 \pm 0.6^*$ and $4.8 \pm 0.4^*$, $2.4 \pm 0.5^*$ nmol/60 min/ 10^5 cells for stretch vs control and stretch plus nifedipine (10^{-7} and 10^{-6} M), respectively; $n=6$; $*P < 0.05$ vs stretch].

This antioxidant activity of nifedipine may exert vascular protective effects in human endothelial cells. Thus, nifedipine may affect mechanical forces which, as determinants of the balance between nitric oxide and superoxide anion, are likely to play a key role in the pathophysiology of hypertensive vascular disease.

Key Words: Nitric oxide; oxidative stress; mechanical forces